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Review Article

COVID-19: An insight into the developments in diagnostics and therapeutics in India

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ABSTRACT

The unexpected pandemic set off by the novel coronavirus (SARS-CoV2) has spread to more than 210 countries across the globe, including India. In the current pandemic situation, various steps have been taken by the Indian government to prevent and control the spread of the SARS-CoV2 infection. To date, there are no proven vaccines or effective therapeutic interventions against the virus. Current clinical management includes infection prevention and control, symptom-specific relief and supportive care. Physicians and scientists across the country have been tirelessly working on developing effective diagnostic and therapeutic strategies and to combat and control this infection. As the demand for diagnostics and therapeutics continues to rise in India and around the globe, it is essential to rapidly develop various algorithms to successfully identify and contain the virus. This review discusses the updates on the recent developments in COVID-19 diagnostics and therapeutics in India.

Keywords: COVID-19, SARS-COV2, Diagnostic tools, Therapeutic interventions and public health

INTRODUCTION

The coronavirus disease has rapidly spread worldwide within a span of 3 months, transitioning from an epidemic to a pandemic. SARS-CoV2 belongs to the B lineage of the beta-coronaviruses and closely resembles the SARS-CoV virus.[1] Like other viruses, SARS-CoV-2 uses receptor-mediated endocytosis to invade and infect human cells. SARS-CoV2 invades human epithelia cells and causes associated pathophysiology by attaching to the angiotensin-converting enzyme-2, a protective enzyme against lung damage.[2] In India, about 80–85% of patients infected with the COVID-19 virus display a mild-to-moderate course of the disease and spontaneously recover at 14–20 days from the point of the first contact, while about 15% of patients progress to severe stages of the disease, often requiring ICU admission and mechanical ventilation. A recent Indian statistical study reported that the recovery rate increased of patients infected with SARS-CoV2 in India increased to 47.99%, the case load rate decreased to 49.21%, and the death rate was very low at 2.80%.[3] Most of the patients who progress to severe stages of disease belong to the elderly age group <65 years of age and have multiple associated comorbidities.

Although Indians seem to display lower incidence of infections and deaths due to the COVID-19 virus,[4] to date, there are no approved vaccines or drugs to cure the infection caused by this virus.

Table 1: A summary and comparison between key developments in SARS-CoV2 diagnostics.

Parameter	Nucleic acid based[5-7]	Antigen based[5,8,9]	Serology based[5,10]
Target molecule (s)	Viral RNA – different conserved sequence of the genome like 1. *S* gene (spike proteins gene) 2. *M* gene (membrane protein gene) 3. *N* gene (nucleocapsid protein gene) 4. *RdRP* gene (RNA-dependent RNA polymerase gene) in the open reading frame *ORF1ab* region 5. *E* gene (envelope protein gene)	Virus cell surface antigens like 1. Spike proteins (S protein) 2. Membrane protein (M protein) 3. Envelope protein (E proteins)	Presence of IgG or IgM antibody levels in the blood of the infected individual
Specificity	Gold standard method highly specific detection of target pathogens. Sometimes, false positives are expected due to matrix assisted inhibition or impurities in genetic material	Highly specific to the target antigen but cross-reactivity can be expected with the similar group of pathogen due to structural homology in antigens/epitopes	Specific but usually shows cross reactivity with similar group of pathogen due to structural homology in antigens/epitopes
Sensitivity	Highly sensitive; can detect 10 copy/μL target nucleic acid	Moderately sensitive however higher sensitivity can achieved, depends on the reporter probe attached to the revealing antibody	Moderately sensitive but cannot directly detect the viral load in the blood. The assay can only determine whether infection has occurred
Equipment dependent	These assays are instrument dependent. It requires equipment (thermal cycler) which is technologically intensive. However, isothermal-based amplification assay can be performed in water bath or in heat block	For qualitative analysis or for yes/no type test can be achieved without equipment; for quantitative analysis, equipment is required	Sometimes, these assays employ equipment for quantitative analysis or in comparison studies. However, equipments are not mandatory
Time to results	Times based on the selected method for PCR amplification is chosen. Typically, PCR-based test can be completed in <3 h. However, isothermal-based amplification can be achieved <20–30 min	These tests can be completed from 3 hours to 10 minutes. ELISA like assay takes about 2–3 hours whereas lateral flow assay or dipstick-based assay can be completed in <10 min	ELISA like platforms would take about 2–3 hours. However, lateral flow-based assay takes 10–15 minutes.
Technical skills required	Yes. Require educated skilled personal to perform the experiments and analysis of work	Yes. Require technical skill persons in handling the pipette needed and operating the equipment. However, lateral flow-based assay can be performed by layman	Yes. Technical skills persons are required in pipetting the reagents and perform the assays and operating the equipment. However, performing lateral flow assays not required any technical skilled person
Reagents	These tests use expensive and sensitive reagents which are not readily available every time, moreover, it is required expensive facility and expertise to manufacture these reagents	Relatively low-cost and simpler reagents are involved. But need time, proper facility and expertise to manufacture these reagents	Relatively low-cost reagents are involved. But need time, facility, and expertise to manufacture these reagents
Affordability	Most of the assays are costly due to involvement of costly reagents, equipment, and technical expertise	Most of the tests affordable	Most of the test are affordable
Diversification of products	A number of diversified/variations of nucleic acid-based kits are available	Moderately diversified/variations are exist	Limited
Location-specific operation	These tests only can be performed in well-equipped laboratory and other out-and-out facilities as the RNA is highly sensitive and the test reagents are also sensitive to temperature, light and environmental conditions, and contamination	These methods are relatively rugged. Some of them can be operated in fields, bed side, and homes. However, the viral particles need to be inactivated before performing these tests	These test methods are rough. They can be operated open home or bed side of the patient
Examples	PCR, RT-PCR, isothermal PCR (LAMP, RAMP)	ELISA, lateral flow assays, dipstick, immuno-PCR	ELISA, lateral flow

At present, supportive care and symptom-based treatments are the only solutions.

TRENDS IN DIAGNOSTICS

Early and effective diagnosis is critical to positive disease prognosis and outbreak control. Due to the growing pandemic and shortage of rapid molecular testing, several laboratories and diagnostics developers around the globe have innovated and developed different diagnostic tools. Table 1 serves to summarize recent global advances in SARS-CoV2 diagnosis. At present, employed methods of diagnosis include CT scans and reverse-transcription real-time PCR. The two possible molecular approaches toward detection of the pathogen follow either nucleotide or antigen routes. Retrospectively, the viral infection can also be indirectly detected by identifying the IgG/IgM antibodies generated specific to the viral antigens. The selection of the appropriate test has to be weighed up on their certain advantages and limitations.

Diagnostic tests development in India

COVID KAVACH ELISA was developed by National Institute of Virology, Pune, India, by isolating virus from tested positive patients. The kit is manufactured by Zydus-Cadila which is the leading global pharmaceutical company in India. The Indian Council of Medical Research (ICMR) has approved this kit. The kit is reported to have 98.7% sensitivity and 100% specificity. As per the ICMR officials, the kit will be used in a national wide serosurvey conducted by the Health Ministry.[11] GCC Biotech India Pvt. Ltd. has developed an indigenous low-cost COVID-19 test kit after rigorous clinical trial. It has high accuracy and can deliver results in <90 min. The firm has received the approval of ICMR.[12] Quanitplus COVID-19 is an ICMR approved testing kit developed by Huwel Lifesciences from Hyderabad. The kit can deliver results within 2 h. It is a single formulation which does not require any addition of separate component while setting up reactions.[13]

The local companies authorized by the Central Drugs Standard Control Organization to develop diagnostics kits are Mylab, Medsource Ozone Biomedicals, Voxtur Bio, and Alpine Biomedicals.[14] Apart from these, many start-ups in different parts of the company are developing rapid, accurate, affordable diagnostics kits. Noida-based DNA Xperts have developed RT-PCR which can deliver the results in 58 min, cut the current testing time of 2 to 3 h. This kit is awaiting the ICMR approval.[15] Sree Chitra Tirunal Institute for Medical Sciences and Technology in Thiruvananthapuram has developed an innovative diagnostic test kit named Chitra Gene LAMP-N for the diagnosis of SARS-CoV-2. This detects the N-Gene of virus using reverse transcriptase loop-mediated amplification of viral nucleic acid or RT-LAMP technique. This kit is considered as one of the first few confirmatory diagnostic tests for N-gene of SARS-CoV-2 virus using the RT-LAMP technique in the world. The test is highly specific that it can detect two regions of the gene which will ensure that the test does not fail even if one region of the viral gene undergoes mutation during its current spread. The detection time is only 10 min. The sample to result time is <2 hours.[16]

Challenges and future directions

Although there are ample types of diagnostic kits in the market, their affordability and accessibility remain a major challenge, especially in countries like India. A few reasons for this include – non-availability of required reagents, lack of technical expertise to perform the test and operate the equipment, and limited accessibility to research facilities to acquire access to the virus samples. There are also significant constraints in meeting the medical requirements in terms of speed, volume, and cost of the diagnostic tools. One way to address this issue would be to enforce the "ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) Criteria" as a benchmark for developing and identifying the most appropriate diagnostic tests for resource-constrained settings.[17]

TRENDS IN COVID-19 THERAPEUTICS

On successful diagnosis of the disease, it is important to have effective treatments in place that help alleviate symptoms and improve prognosis. In India, we are currently working toward testing spectrum-specific therapeutic interventions in SARS-CoV2 treatment.[18] The following section serves to offer you a brief insight into these interventions. They are all under investigation and are being tested through clinical trials.

Cytokine therapy: Mild-moderate cases

On infection by SARS-CoV2, the innate arm of the immune system is triggered as the first line of defense, and this induces the expression and release of Type I interferons (IFNs) and other pro-inflammatory cytokines.[19] Among these, IFNs exhibit potent antiviral activity by acting as signaling molecules to activate the required cellular/genetic machinery (e.g., immunomodulatory genes) to result in the production of antiviral proteins, which go to elicit effector functions such as the inhibition of viral replication.[20]

However, these innate responses are not always successful in eliminating the virus. In such cases, the adaptive arm of the immune system takes over, and this is usually around the 4^{th}–7^{th} day post-infection. A successful transition to an

adaptive immune response relies on: (a) The presence of required cytokine (IFNs and ILs) cues from innate immune cells and (b) the presence of an adequately large T-cell repertoire.[21] A compromise in either of these results in immune evasion and associated pathophysiology. SARS-CoV2, through the action of several of its virulence factors, eventually leads to the inhibition of IFN-I production and functioning. Moreover, age-related degeneration of the thymic epithelium results in loss of thymic function due to a reduction in size and diversity of the naïve T-cell repertoire, which leads to weakened immune surveillance mechanisms in the elderly, increasing their susceptibility to and mortality from the infection.[22] Thus, by stimulating the innate immune responses to trigger IFN production and release at early stages of the disease, we could effectively bridge the gap between the innate and adaptive immunity, and this would significantly improve prognosis and survival. This can be achieved by administration of IFNs.

A team of doctors at HCG, Bengaluru, has developed a novel cytokine cocktail containing INF-gamma (1000–2000 pg/ml) and interleukin-6 (IL-6) 500–750 pg/ml. We propose that this cocktail, when administered to an infected patient, can result in a surge of cytokines in the body of the infected person and will boost his ability to fight the virus. They are currently evaluating the safety and efficacy of this cytokine cocktail through Phase I clinical trials where 1 ml of the study cytokine preparation will be administered as an intramuscular injection once a day for up to 10 days to patients with mild/moderate disease.

Convalescent plasma (CP) therapy: Severe cases

Severe pneumonia caused by SARS-CoV2 is characterized by rapid viral replication, massive inflammatory cell infiltration, and elevated pro-inflammatory cytokines, cytokine storm culminating in virtually irreversible lung injury.[23] This severe form of the SARS-CoV2 infection is known to lead to lymphopenia with elevated cytokines, including IL-6, IL-10, TNF-α, and granulocyte-macrophage colony-stimulating factor.

Drawing on current data and literature on the use of CP in SARS-CoV2, it is clear that (a) CP therapy helps reduce mortality in severely ill patients, (b) an increase in neutralizing antibody titers and disappearance of SARS-CoV-2 RNA was observed in almost all the patients after CPT therapy, and (c) there was a clear improvement of clinical symptoms post CP therapy.[24] Thus, based on available yet limited scientific data, the administration of CP to severely ill-COVID-19 patients appears safe, clinically effective, and reduces mortality. The US-FDA has approved the use of CP in patients with COVID-19 on account of its beneficial effects, and the ICMR has approved several CP therapy trials in India.[25]

In SARS-CoV2, viremia peaks in the 1st week of infection. This generates a primary immune response within days which is followed by virus clearance. CP therapy relies on the administration of plasma (rich in specific IgG and IgM anti-SARS-CoV-19 antibodies) isolated from recovered individuals to severely ill patients. This suppresses viremia and blocks new infection by accelerating infected cell clearance.[24] CP therapy would thus be particularly beneficial to severely ill patients who have not responded to other drugs/treatments, have developed (ARDS), and pose an increased risk organ failure. It might also help keep who are moderately ill patients and individuals comorbid chronic medical conditions, from becoming more ill and experiencing further complications. Current research is also evaluating the potential of CP therapy as a preventive intervention that could be administered to health care workers exposed to someone with COVID-19 to potentially prevent them from getting COVID-19.[26]

Considering the current research and proven efficacy of CP in the past epidemics, a team of doctors at HCG, Bengaluru, has proposed a clinical trial to use CP therapy in patients diagnosed with COVID-19. Patients who have recovered from SARS-COV2 and who have been discharged from SARS-CoV2 treatment centers or units could be potential donors for CP which would be rich in immunoglobulins against SARS CoV2. The objective of their current study/clinical trial is to investigate the potential use of CP in patients with coronavirus SARS-CoV-2 infection compared to standard care.

Mesenchymal stem cells: Critical cases

In critically ill COVID-19 patients, a lot of the symptoms are caused due to an overactive innate immune response (e.g., cytokine storms) that comes into play due to a dysfunctional adaptive immune response.[27] Thus, the immunomodulatory effect of mesenchymal stem cells could potentially be implemented as a therapeutic intervention in critically ill or likely to be critically ill patients to help manage their symptoms and reduce risk of disease progression. There have been a few recent studies that have served to understand the therapeutic role of MSCs in respiratory infections similar to SARS-CoV2 and have displayed promising results.[28]

Mesenchymal stem cells derived from umbilical cord, dental pulp, bone marrow, etc., have been used for immune modulation in various autoimmune disorders.[29] The characteristic property of MSCs is that they aid tissue regeneration and repair. On account of low MHC expression, MSCs are a relatively non-immunogenic population of cells, making them ideal for therapeutic interventions using allogenic transfers without HLA matching.[30] Interestingly, the pro-inflammatory cytokines released during this hyperactive immune response elicit anti-inflammatory effects

on the MSCs.[31] This results in the MSCs secreting several soluble factors such as nitric oxide, transforming growth factor beta, prostaglandin E2, indoleamine 2,3-dioxygenase, HLA-G5, and soluble IL-6, which function to inhibit the proliferation and activation of pro-inflammatory cells such as TH1 and TH17, thereby decreasing the production of pro-inflammatory cytokines such as IFN-gamma and IL-17. Mesenchymal stem cells also inhibit the activation of cytotoxic T-cells and dendritic cell subsets, thereby reducing direct injury to lung parenchyma by increased regulation of T-Reg activity and production and release of anti-inflammatory cytokines such as IL-10.[32] The lifespan, potential, and efficacy of MSCs can be controlled by priming the MSCs with IFN-gamma before transfusion.[33]

Thus, to explore the use of mesenchymal stem cells in the treatment of COVID-positive patients with severe disease, a team of doctors at HCG, Bengaluru, has initiated a clinical trial to transfuse allogeneic mesenchymal stem cells derived from donated bone marrow or umbilical cord administered through intrapulmonary implantation where possible or administered through the intravenous route. To offset the neutralization of MSCs, we have proposed priming of MSC with a cytokine cocktail derived from Th1 cells of healthy donors to suppress the hyperactive immune response and promote tissue repair.

CONCLUSION

As the number of individuals infected with SARS-CoV-2 continues to rise in India, health-care systems are facing increased pressure. In such a situation, rapid diagnostics, vaccines, and therapeutics become crucial in the control and management of the pandemic. Early diagnosis of COVID-19 allows for timely medical intervention, enhancing disease prognosis and infection control. At present, cytokine therapy and CP therapy constitute some of the most promising interventions in the treatment of COVID-19 patients. While the safety of efficacy of these treatments is being assessed by clinical trials, the Indian government continues to implement public measures for disease prevention and control such social distancing and self-quarantine. There have also been several guidelines published for protecting Indian health care workers from contamination during COVID-19 pandemic.[34]

The Ministry of AYUSH in India has also issued self-care guidelines and preventive health measures to boost immunity with special references to respiratory health, based off Ayurvedic research and literature.[35] Recently, the Indian government also recommended the use of hydroxychloroquine as a preventive measure to protect frontline workers from the SARS-CoV2 infection. This stands controversial as health and safety concerns have prompted several countries across the globe to reconsider the controversial use of this drug. In addition, findings from recent studies deem this recommendation as premature and risky due to the lack of evidence supporting hydroxychloroquine's efficacy against the new coronavirus and suggest that the use of this drug can trigger serious side effects.[36]

It is thus essential to move carefully forward with all the available information to effectively deal with the current and future face of this pandemic.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

The author Ashish Gulia is on the editorial board, and does not have any competing interests.

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